REMARKS

Claims 1-5, 7-11, 13-17, 19-23 and 25-55 were pending in the subject application. Claims 1-5, 7-11, 13-17, 20, 22-42, and 46-51 have been canceled without prejudice, claims 44-45 and 54-55 are withdrawn, claims 56-70 are not entered, claims 19, 21, 43, 44, 45, and 52-55 have been amended, and claims 71-78 have been added. No new matter has been added by the claim amendments or additions. Support for the claim amendments may be found throughout the specification. In particular, support for the amendments to claim 19 may be found, for example, at page 8, lines 3-9 and Figure 13, etc. Support for the amendments to claims 43-45 may be found, for example, in Figure 9B and page 23, line 27 to page 24, line 12, etc. Support for claim 71 may be found, for example, at page 5, lines 15-27, page 9, lines 13-19, and page 17, lines 17-22, etc. Support for claim 72 may be found, for example, at page 9, lines 13-19, page 16, line 29 to page 17, line 4, and page 18, line 22 to page 19, line 6, etc. Support for new claim 73 may be found, for example, at page 9, lines 5-12, etc. Support for new claim 74 may be found, for example, at page 9, lines 20-26, etc. Support for new claims 75-77 may be found, for example, in Figure 9B and page 23, line 27 to page 24, line 12, etc. Support for new claim 78 may be found, for example, at page 17, lines 9-12 and page 17, lines 17-22.

As requested by the Examiner, the text of the claims designated as "not entered" has been removed and the subject matter of the non-entered claims has been represented as new claims 71-77. The Examiner is respectfully requested to enter and examine the new claims.

The claim amendments are fully supported by the specification and introduce no new matter. Amendment or cancellation of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants expressly reserve the right to pursue any cancelled subject matter in this application or in subsequent applications that claim benefit of this application.

Specification

The specification has been amended as suggested by the Office Action. Trademarks have been demarcated in the appropriate format, and minor errors in the specification have been corrected.

Claim Objections

The Office Action states on page 8, in paragraph 11, that claims 7-9, 13-15, 19-21, 25-48 and 53-55 are objected to as being drawn to the subject matter of non-elected inventions. However elsewhere in the Office Action it was stated that the restriction requirement between Groups I and III had been withdrawn (see page 5, paragraph 7) and page 1 of the Office Action lists the above-referenced claims as being rejected rather than withdrawn. Applicants have treated those claims as pending except for claims 44, 45, 54 and 55 which Applicants are treating as withdrawn because they refer to nonelected sequences. Additionally, Applicants have canceled others of these claims by this Amendment. It is requested that the Examiner clarify this point.

Written Description—35 USC § 112, second paragraph

A. The Office Action asserts that claims 1-3, 7-9, 13-15, 19-21, and 25-55 are indefinite because of the use of the term "OX-2/CD200" or "CD200." In particular, the Office Action states that the terms OX-2 or CD200 may be used to refer to OX-2 or CD200 proteins from different species which is alleged to render the claim indefinite. Applicants respectfully disagree with the rejection. In particular, Applicants submit that a person of ordinary skill in the art would understand the claims as written. The claims are directed to treating a subject with upregulated OX-2/CD200 by administering to the subject an antibody that binds to the OX-2/CD200. Clearly one of ordinary skill in the art would understand that the OX-2/CD200 protein being referred to in the claim is the OX-2/CD200 protein from the subject being treated, e.g., human OX-2/CD200 when the subject is a human, and that the antibody used to treat the subject is an antibody that binds to the OX-2/CD200 from the subject, e.g., an antibody that binds to human OX-2/CD200 when the subject is a human. However, solely to expedite prosecution of the subject application, Applicants have amended the claims to specify that the subject is a human and that the antibody binds to human OX-2/CD200.

In addition, because some claims recite both "OX-2/CD200" and "CD200," the Office Action contends that it is unclear if these terms are meant to identify one and the same protein or two different proteins. Applicants submit that the terms "OX-2" and "CD200" are interchangeably used in the field. However, solely to expedite prosecution, Applicants have amended the claims to unify the language and recite "OX-2/CD200" for all references to the subject protein.

Such amendments are believed to fully address the rejection of claims 1-3, 7-9, 13-15, 19-21, and 25-55 under 35 USC §112, second paragraph. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

B. The Office Action asserts that claims 1-3, 7-9, 13-15, 19-21, and 25-55 are indefinite because of the recitation in claims 1, 7, 13, 19, and 49-51 of the limitation "the immune-suppressing effect of OX-2/CD200." The Office Action alleges that because OX-2/CD200 has multiple effects that suppress the immune system, it is unclear to which effect these claims are directed. Applicants respectfully disagree with the rejection. However, solely to expedite prosecution, the claims have been amended to specify "an immune-suppressing effect of OX-2/CD200." Such amendments are believed to fully address the rejection. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Written Description—35 USC § 112, first paragraph

A. Claims 1-3, 7-9, 13-15, 19-21, and 21-55 are rejected as allegedly failing to comply with the written description requirement. Specifically, the Office Action states that "the specification only adequately describes antibodies that specifically bind to the human OX-2/CD200 protein that comprise CDRs consisting of all of the 6 complementarity determining regions (CDRs) of the scFv-9 antibody" (Office Action page 12, first paragraph). Applicants respectfully disagree and submit that such a standard, e.g., that only a single antibody having six specifically defined CDR sequences may be claimed, is clearly inconsistent with the written description guidelines. Example 16 of the Revised Interim Written Description Guidelines Training Materials (the "Guidelines"), states that:

> Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five

> classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature, one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X.

Accordingly, as long as a fully characterized antigen is disclosed, the specification is sufficient to provide written description support for claims directed to antibodies that bind the antigen even if no antibodies were actually made. In particular, such a disclosure provides written description for the full range of antibodies that bind to that antigen without any sort of sequence limitation. In Example 16 of the Guidelines, a "fully characterized antigen" with well-defined structural characteristics is deemed to be provided upon disclosure of (i) isolation of the antigen, (ii) molecular weight of the antigen, and (iii) a method for purification of the antigen. Using this standard, the instant application clearly meets, and even exceeds, the standard for adequate written description. The instant application describes isolation of CD200, the molecular weight of CD200 (e.g., 50 kD), and a method for isolating CD200 (e.g., by immunoprecipitation with the scFv-9 antibody) (see e.g., paragraph [0123] of the published application).

Based on the remarks above, Applicants submit that the instant application clearly provides adequate support for the full scope of antibodies with well-defined structural characteristics that bind to CD200. However, Applicants are not claiming the full scope of anti-CD200 antibodies. Rather, Applicants are claiming a specific subset of antibodies that is further defined functionally. In particular, the claims are directed to antibodies, or antigen binding fragments thereof, that bind to OX-2/CD200 and effectively inhibit an immune-suppressing effect of OX-2/CD200. As presented above, since the full complement of anti-CD200 antibodies is adequately supported by the instant application, Applicants submit that the claimed subgenus of antibodies is also clearly supported by the specification. In particular, the Examiner's attention is directed to Example 14 of the Guidelines. Example 14 explains that claims to protein variants (which include variants having substitutions, deletions, insertions and additions) having a common structural feature and a specified function find adequate written description support in a specification which discloses (i) that procedures for making protein variants are routine in the art and (ii) an assay for detecting the claimed activity, *even when no examples of variants are actually provided.* Based on this standard, the instant application clearly meets, and even exceeds, the written description standard for the

instant claims. In particular, the claims are directed to a particular subset of anti-CD200 antibodies, or antigen binding fragments thereof, having a common structural feature (e.g., they are antibodies which are structurally well characterized molecules) and a specified function, e.g., inhibition of an immune-suppressing effect of OX-2/CD200. Furthermore, the specification discloses a variety of well known art recognized methods for producing antibodies. Example 16 of the Guidelines specifically states that production of antibodies is a mature technology and the level of skill is high and advanced. Furthermore, the specification provides an assay for identifying antibodies that inhibit an immune-suppressing effect of OX-2/CD200, see e.g., Example 3, in particular paragraph [0138], and Figure 14 of the published application. Using the assay in Example 3, one of ordinary skill can readily determine whether a specific anti-CD200 antibody can restore a Th1 response (i.e., inhibit an immune-suppressing effect of OX-2/CD200). Accordingly, the application clearly meets the requirements for an adequate written description as provided in the Guidelines.

Therefore, in view of Examples 14 and 16 of the Guidelines and the extensive description and working examples provided in the specification, Applicants have clearly provided sufficient written description for the instant claims. The claims cover a structurally well characterized class of proteins (e.g., antibodies) and the specification provides assays for identifying all of the antibodies which have the specified activity. Furthermore, Applicants provide at least one working example that is representative of the claimed genus. Accordingly, one of skill in the art would conclude that Applicants were in possession of the necessary common attributes possessed by the members of the genus. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claims 1-3, 7-9, 13-15, 25-42, 49-50, and 52-55 are rejected as allegedly failing to comply with the written description requirement. Specifically, the Office Action asserts that because OX-2/CD200 is upregulated in some cancers, but not others, one cannot predict which of the "subjects with upregulated OX-2/CD200" encompassed by the claims would benefit from treatments that inhibit OX-2/CD200. Applicants respectfully disagree. However, solely in an effort to expedite prosecution, claims 1-3, 7-9, 13-15, 25-42 and 49-50 have been canceled thereby obviating the rejection with respect to these claims. Claims 52-55 have been amended to depend directly or indirectly from claim 19 which was not subject to the rejection. Accordingly, all of the

pending claims are directed to subject matter acknowledged by the Examiner as being adequately described by the instant application. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Enablement—35 USC § 112, first paragraph

Claims 1-3, 7-9, 13-15, 19-21, and 25-55 are rejected as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

As an initial matter, Applicants note that the amended claims relate specifically to the use of anti-CD200 antibodies to treat CLL. Such amendments are believed to fully address the Examiner's concerns that the claims are drawn to methods with no intended use (see page 21 of the Office Action). Similarly, the amendments are believed to fully address the Examiner's concerns about the patient population to be treated (see e.g., page 21 of the Office Action). In particular, the amended claims are drawn to methods for treating a specific indication, namely CLL, and a specific patient population, namely CLL patients having upregulated OX-2/CD200.

Applicants submit that the instant application provides extensive disclosure that clearly enables one of ordinary skill in the art to carry out the claimed methods. For example, the specification discloses that OX-2/CD200 is upregulated on CLL cells (see e.g., Figure 8c and paragraphs [0120]-[0123] of the published application). The specification also teaches that subjects suffering from CLL may be screened to determine whether the subject has upregulated CD200 (see e.g., paragraph [0038]). The application further teaches that such subjects may be treated by administration of an anti-OX-2/CD200 antibody (see e.g., paragraph [0086]). CDR sequences for several anti-OX-2/CD200 antibodies are provided (see e.g., Figure 9B). In addition, the specification discloses that since CLL cells overexpressing OX-2/CD200 greatly diminish the production of Th1 cytokines, the administration of an anti-CD200 antibody will restore the Th1 cytokine profile in CLL subjects having upregulated OX-2/CD200 (see e.g., paragraph [0086]). Reversal of the cytokine shift to a Th1 profile has been demonstrated to augment the anti-tumor effects of T cells (see e.g., paragraph [0008]). Therefore, the specification clearly demonstrates that anti-OX-2/CD200 antibodies are useful therapeutic agents for treating CLL in which OX-2/CD200 is upregulated.

In addition to these teachings, the specification provides working examples showing that anti-OX-2/CD200 antibodies are capable of restoring the Th1 cytokine profile. In particular the Examiner's attention is directed to Example 3 at paragraph [0129]-[0139] which discloses the results of a mixed lymphocyte reaction which was used to evaluate the effects of Th1 cytokine production. The Example discloses that the presence of OX-2/CD200 transfected but not untransfected cells results in a down-regulation of Th1 cytokines. Addition of an anti-CD200 antibody at 30 μg/ml fully restored the Th1 response, indicating that the antibody blocked interaction of OX-2/CD200 with its receptor (see e.g., paragraph [00138]). Although this is an *in vitro* assay, it replicates what occurs *in vivo*, i.e., there are interactions between CD200 and its receptors on lymphocytes which modulate the immune response. Prevention of such interactions, such as by binding an antibody to CD200, would therefore be expected to similarly effect the *in vivo* immune response. Accordingly, Applicants submit that the instant application provides sufficient disclosure and working examples that would enable one of skill in the art to carry out the claimed methods.

Furthermore, the sufficiency of the enabling disclosure of the instant application is evidenced by the results of *in vivo* experiments presented in Applicant's related applications USSN 10/894,672 (US 2005/0074452) and USSN 11/171,567 (US 2006/0057651). For example, USSN 10/894,672 describes the results of experiments conducted in an animal model to test the effects of an anti-OX-2/CD200 antibody on tumor rejection (see paragraphs [0162]-[0165] of US 2005/0074452). These results demonstrate that administration of an anti-CD200 antibody to NOD/SCID mice that have been injected with RAJI lymphoma tumor cells expressing CD200 results in tumor rejection or slower tumor growth (see paragraph [0165] of US 2005/0074452). Similarly, USSN 11/171,567 describes the results of several experiments conducted in a mouse model using two different lymphoma cell lines, Raji and Namalwa, overexpressing CD200 (see e.g., paragraphs [0244]-[0270] of US 2006/0057651). These results demonstrate that anti-OX-2/CD200 antibodies reduced tumor volume by 50-75% in the Raji model and by up to 97% in the Namalwa model (see e.g., paragraphs [0252] and [0261] of US 2006/0057651). Accordingly, these results demonstrate that the teachings provided in the instant application clearly enable one of skill in the art to practice the claimed methods without undue experimentation.

The Office Action asserts that the field of anticancer drug discovery is highly unpredictable and therefore one cannot extrapolate from *in vitro* or even *in vivo* mouse data to the applicability for treatment in humans. Applicants respectfully submit that no showing of treatment of a human being is required to support operability of claims directed to methods of treating disease. See, e.g., *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). Moreover, *in vivo* data is not required to enable an *in vivo* use. Rather, use of *in vitro* data may be sufficient to show the required utility (see *Cross v. Iizuka*, 753 F.2d 1040, 1046-1047 (Fed. Cir., 1985) *citing Nelson V. Bowler*, 626 F.2d 853 (Fed. Cir. 1980)). An *in vitro* model or animal based evidence that is reasonably predictive is sufficient (*In re Brana*). A rigorous or an invariable exact correlation between *in vitro* utility and *in vivo* activity is not required for purposes of enablement (see MPEP 2164.02 *citing Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985)). In view of the *in vitro* examples provided in the present application, Applicants submit that the instant application clearly provides sufficient support to enable the currently pending claims. Furthermore, as discussed above, Applicants have demonstrated that the *in vitro* results presented in the instant application are predictive of the *in vivo* anti-tumor effects of the anit-OX-2/CD200 antibodies.

In addition, Applicants note that the references cited as supportive of the unpredicatability in the field of cancer drug discovery would not cause one of skill in the art to doubt the predictive value of the experimental results provided in the instant application. In particular, the Gura et al. reference is actually supportive of *in vitro* screening for novel cancer drugs (see e.g., page 1042, first column). The passage in Zips et al. that was relied upon is not applicable to the methods of the instant application. In particular, Zips is used to support the unpredicatability of *in vitro* data to *in vivo* effects. However, the cited passage in Zips is discussing the difficulty of replicating the 3-dimensional conformation of a tumor *in vitro*. In contrast to the situation in Zips, the instant application is directed to leukemia, a blood borne cancer, and thus it is not apparent how difficulties encountered due to the complexities of solid tumors are applicable to leukemia. Dennis is relied on in an effort to cast doubt on the value of mouse models of cancer. Applicants note that no animal models are 100% predictive of human therapeutics and the art is constantly striving to develop better models. However, the desire for better models does not undercut the value of the current model systems. Dennis was published in 2006, after the filing date of the instant application, and

discusses ways in which mouse models may be improved in the future. Applicants submit that they should not be held to a standard which requires use of a model system not developed at the time the application was filed let alone several years thereafter. The instant application provided enablement for the pending claims using art recognized models that were available at the time the application was filed. Finally, Srivastava was similarly pointed to as undercutting the value of mouse models. Applicants note that Srivastava is directed to the field of cancer immunity which the author states poses "a unique hurdle" (see page 364, lower left column). It is not clear how the field of cancer immunity is relevant to the treatment methods claimed in the instant application. Accordingly, Applicants submit that cited references would not have caused one of skill in the art to doubt the predictability of the results provided in the instant application.

Based on the above remarks, Applicants submit that the currently claimed methods meet the enablement requirements under 35 USC §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 1-3, 7-9, 13-15, 19-21, and 49-55 are provisionally rejected on the basis of obviousness-type double patenting over claims 50-54 of copending Application No. 10/379,151. Applicants request that the Examiner hold the provisional rejections made under the judicially created doctrine of obviousness-type double patenting in abeyance until otherwise allowable subject matter is identified in the instant application. Once allowable subject matter has been identified, Applicants will evaluate the filing of a terminal disclaimer or providing arguments in view of the claims pending at that time.

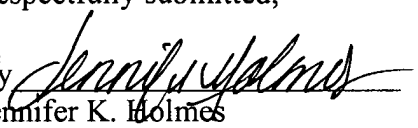
Submitted concurrently herewith is a Statement Under 37 CFR §1.78(c) by Assignee indicating that U.S. Patent Application Nos. 10/736,188 and 10/379,151 were commonly owned or subject to an obligation of assignment to Alexion Pharmaceuticals, Inc. at the time the later invention was made. This submission precludes a rejection of the instant claims under 35 USC §103(a) based upon the commonly assigned case.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. A petition for a two month extension of time and appropriate fee are submitted concurrently herewith. Should any additional extensions of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. ALEX-P03-060.**

Dated: December 27, 2007

Respectfully submitted,

By 

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